Clinicians' Attitude to Doublet Plus Anti-EGFR Versus Triplet Plus Bevacizumab as First-line Treatment in Left-Sided *RAS* and *BRAF* Wild-Type Metastatic Colorectal Cancer Patients: A Multicenter, "Real-Life", Case-Control Study

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Abstract

With no data from directly comparing trials, in this multicenter, retrospective, "real-life", case-control study of clinicians' attitude conducted on 718 left-sided *RAS*/*BRAF* wild-type metastatic colorectal cancer patients, a triplet plus bevacizumab regimen seemed to be at least equally active and effective compared to a doublet plus anti-EGFR regimen, especially in younger patients, with good ECOG-PS and liver-limited disease.

Background: Doublets plus antiepidermal growth factor receptors monoclonal antibodies (EGFRi) are widely considered the preferable first-line regimen in patients with left-sided *RAS*/*BRAF* wild-type metastatic colorectal cancer

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Submitted: Mar 2, 2021; Revised: Jul 6, 2021; Accepted: Jul 6, 2021; Epub: xxx

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https://doi.org/10.1016/j.clcc.2021.07.003

Please cite this article as: Alessandro Parisi et al, Clinicians' Attitude to Doublet Plus Anti-EGFR Versus Triplet Plus Bevacizumab as First-line Treatment in Left-Sided RAS and BRAF Wild-Type Metastatic Colorectal Cancer Patients: A Multicenter, "Real-Life", Case-Control Study, Clinical Colorectal Cancer,

(mCRC), resulting superior in terms of activity and efficacy compared to doublets plus bevacizumab. However, data comparing doublet plus EGFRi and triplet plus bevacizumab are lacking, and the relative benefit of an intensive regimen plus an antiangiogenic backbone in this population is debated. **Methods:** This multicenter, retrospective study aimed at evaluating clinicians' attitude to triplet-bevacizumab and doublet-EGFRi as first-line regimen in patients with left-sided *RAS*/*BRAF* wild-type mCRC treated in clinical practice at 22 Oncology Units from March 2012 to October 2020. A random case-control matching was performed to compare activity (ORR), and effectiveness (PFS, OS, secondary resection rate of metastases with curative intent) between triplet-bevacizumab and doublet-EGFRi, on the basis of ECOG-PS, age, gender, and burden of disease. **Results:** A total of 718 patients were consecutively treated with doublet-EGFRi (686, 95.5%) or triplet-bevacizumab (32, 4.5%). After case-control matching, median PFS was 13.6 (95% CI, 8.9-31.7) and 16.1 (95% CI, 12.1-36.8) months (P= .621), while median OS was 30.2 (95% CI, 14.4-69.5) and 38.1 (95% CI, 33.1-101.1) months (P= .0283) in the doublet-EGFRi and the triplet-bevacizumab cohort, respectively. The ORR was 65.6% and 90.6% (P= .016), while the secondary resection rate was 18.8% and 46.9% (P= .016), in the doublet-EGFRi and the triplet-bevacizumab cohort, respectively. Triplet-bevacizumab was associated with a higher incidence of G3/G4 neutropenia (25.0% vs. 12.5%, P= .041). **Conclusion:** Although a doublet-EGFRi remains the recommended upfront regimen in patients with left-sided *RAS* and *BRAF* wild-type mCRC, our real life data suggest a triplet-bevacizumab might be at least equally active and effective in properly selected cases.

Clinical Colorectal Cancer, Vol. 000, No.xxx, 1–8
Keywords: Cetuximab, FOLFIRI, FOLFOXIRI, FOLFOX, mCRC, Panitumumab

Introduction

According to major guidelines, the preferred option as first-line treatment of unresectable left-sided *RAS* and *BRAF* wild-type metastatic colorectal cancer (mCRC) patients is represented by a cytotoxic fluoropyrimidine-based doublet (FOLFOX or FOLFIRI) in association with an anti-Epidermal Growth Factor Receptor (EGFRi) monoclonal antibody (ie, cetuximab or panitumumab).[1-3] In this regard, a landmark retrospective pooled analysis of 6 randomized phase III trials showed a significant survival benefit for doublet plus EGFRi compared to doublet plus bevacizumab in *RAS* wild-type tumors originating from the left side of the colon.[4] These data are confirmed in real-life populations and are supported by genomic and transcriptomic analysis showing a lower incidence of molecular mechanisms of primary resistance to EGFRi in left-sided compared to right-sided CRC.[5-7] In properly selected mCRC patients, particularly in right-sided and/or *RAS* or *BRAF* mutated cases, a triplet chemotherapy (FOLFOXIRI) plus bevacizumab showed to increase response rate and survival compared to doublet plus bevacizumab.[1,8-12] Consistently, as sidedness has never been included as stratification factor in clinical trials investigating the role of a triplet plus bevacizumab as first or subsequent line of treatment, the rate of left-sided *RAS* and *BRAF* wild-type mCRC patients enrolled was very low. However, an intensive regimen as well as an antiangiogenic strategy, demonstrated to be effective regardless of primary tumor location and *RAS* and *BRAF* mutational status.[13-15] As no evidence from clinical trials comparing doublet plus EGFRi versus triplet plus bevacizumab as first line treatment for unresectable left-sided *RAS* and *BRAF* wild-type mCRC are available, we performed a retrospective multicenter analysis to investigate the clinicians' attitude to the 2 regimens in a real-life setting.

Materials and Methods

Patient Eligibility

This retrospective analysis evaluated consecutive *RAS* and *BRAF* wild-type left-sided mCRC patients, either treated with first line doublet chemotherapy plus an EGFRi or with triplet chemotherapy plus bevacizumab, at 21 Italian and 1 Spanish institutions (Supplementary file 1), from March 2012 to October 2020.

Eligibility criteria were: age ≥18 years; histologically confirmed diagnosis of CRC originating from the splenic flexure, descending colon, sigma, and rectum; confirmed *KRAS* (exons 2, 3, 4), *NRAS* (exons 2, 3, 4), and *BRAF* (V600E) wild-type genotype; having received at least one cycle of a first-line treatment with an EGFRi-based doublet (FOLFOX or FOLFIRI) or a bevacizumab-based triplet (FOLFOXIRI).

All patients alive at the time of data collection provided informed consent to participate to this retrospective observational noninterventional study. The procedures followed were in accordance with the precepts of Good Clinical Practice and the declaration of Helsinki. The study was approved by the respective local ethical committees on human experimentation of each institution, after previous approval by the coordinating center (Comitato Etico delle Province di L'Aquila e Teramo, protocol number 21, approved on July 16, 2020).

Study Design

This is a retrospective, multicenter, observational study, aimed at evaluating the clinician's attitude to adopt a doublet plus EGFRi or a triplet plus bevacizumab as first-line regimen in left-sided *RAS/BRAF* wild-type mCRC patients. The measured activity, effectiveness, and safety clinical outcomes were objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and chemotherapy-related adverse events (AEs). Tumor burden at baseline was assessed according to the European Society for Medical Oncology definition.[1] Among patients who underwent secondary curative R0-R1 resection of metastases, an exploratory analysis was conducted on postresection PFS and OS. Patients were assessed with radiological imaging as per clinical practice, with a frequency ranging from 8 to 12 weeks. Baseline resectability of both liver and extrahepatic metastases was assessed by surgeons, radiologists, and

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oncologists at each centre, within or outside a defined multidisciplinary team, according to the local clinical practice. Secondary resection rate was defined as the percentage of patients deemed to be unresectable or borderline resectable at baseline for metastatic disease because of technical or biological factors, and converted to radical (R0/R1) surgery with or without the integration of other ablative locoregional treatments, after a systemic induction treatment. Disease responses were evaluated with the RECIST criteria (version 1.1).[16] Only patients with measurable disease at baseline assessment were included in the activity analysis. ORR was defined as the proportion of patients experiencing a partial or complete response as best overall response. PFS was defined as the length of time from the beginning of first line treatment to disease progression or death from any cause; OS, as the length of time between the beginning of first-line treatment to death from any cause; postresection PFS, as the length of time between the secondary radical resection of metastases to disease relapse or death from any cause; postresection OS, as the length of time between the secondary radical resection of metastases to death from any cause. For PFS, as well as for OS, patients without events were censored at the time of the last follow-up. Data cutoff period was October 2020.

For the study purpose, we grouped patients according to the first-line regimen received (triplet plus bevacizumab and doublet plus EGFRi cohorts), and baseline patients' characteristics were compared across the 2 cohorts.

Considering the heavily unbalanced sample size of the 2 cohorts, a random case-control matching was performed to compare the effectiveness of the 2 groups of interest. All the cases (from the triplet plus bevacizumab cohort) and controls (from the doublet plus EGFRi cohort) were randomly paired on the basis of: ECOG-PS (0 vs. 1 vs. 2), age ($<$ vs. $\geq$ the median age of the entire population), gender (male vs. female), and burden of disease (defined through the number of metastatic sites: 1 vs $\geq$1). Subsequently, clinical outcomes of activity (ORR) and efficacy (PFS and OS) have been explored with univariable analysis across the two matched groups.

To simplify research on medical records and synthesize chemotherapy-related AEs, toxicity was defined as the maximum grade (G) toxicity per patient per each class of AEs: hematological (leukopenia, anemia, thrombocytopenia) and non-hematological (nausea, vomiting, mucositis, hand-foot syndrome, asthenia, anorexia, and others). Because of their clinical relevance, diarrhea, and peripheral neuropathy were evaluated individually. Because of the deep differences between EGFRi and bevacizumab class-specific AEs, it was decided not to collect them. AEs were reported for the overall population, registered according to National Cancer Institute Common Terminology Criteria (NCI-CTC) for AEs (version 4 up to January 2018, version 5 from January 2018), and grouped according to severity (G1-2 and G3-4).

Statistical Analysis

As all the considered variables for the random matching were categorized to obtain a perfect matching, caliper width of <1 for the standard deviation was used.[17]

Chi-square and Fisher's exact tests as appropriate were used to compare baseline patients' characteristics, ORR, and the incidence of AEs across the 2 cohorts.

Median PFS, median OS, median postresection PFS and median postresection OS were evaluated using the Kaplan–Meier method and the log-rank test was used for the univariable analysis. Median period of follow-up was calculated through the reverse Kaplan–Meier method. Threshold for statistical significance was set to *P*value = .05. All statistical analyses were performed using MedCalc Statistical Software version 18.11.3 (MedCalc Software Bvba, Ostend, Belgium; http://www.medcalc.org; 2019).

Molecular Profile Assessment

All the molecular analyses were performed according to the local clinical practice of the participating centers. *KRAS, NRAS*, and *BRAF* mutational status was assessed with Sanger sequencing, Real-Time PCR techniques and Next Generation Sequencing (NGS) (such as: OncoGenBasic-S1 kit, Seqplexing; Pyromark Q96 ID System, Qiagen; EasyPGX and Myriapod Colon Status, Diatech Pharmacogenetics; Idylla KRAS and NRAS-BRAF Mutation Test, Biocartis; Ion AmpliSeq Colon and Lung Cancer Panel, Ion Torrent).

Results

Patients Characteristics

Seven hundred eighteen consecutive left-sided *RAS* and *BRAF* wild-type mCRC patients were treated with doublet plus EGFRi (686, 95.5%) or triplet plus bevacizumab (32, 4.5%) as first-line regimen. Patients' features are summarized in Table 1. A triplet plus bevacizumab regimen was carried out in 11 centers. The median age was 63 years (28-84) and no ECOG-PS 2 patients were treated in the triplet plus bevacizumab cohort. Among patients within the doublet plus EGFRi cohort, 275 (40.1%) were treated with FOLFIRI-cetuximab, 48 (7.0%) with FOLFOX-cetuximab, 60 (8.7%) with FOLFIRI-panitumumab, and 303 (44.2%) with FOLFOX-panitumumab. No statistically significant differences were found between the two cohorts regarding disease burden, even if a higher rate of liver-limited disease was found in the triplet plus bevacizumab cohort (59.4% vs. 32.5% in the doublet plus EGFRi cohort, $P = .002$).

Clinical Outcomes Analysis

The median period of follow up for the overall population was 33.8 months (95% CI, 29.9-108.6), while among the doublet plus EGFRi and the triplet plus bevacizumab cohort was 33.4 months (95% CI, 29.1-108.6) and 41.6 months (95% CI, 30.4-68.8), respectively.

ORR, PFS, and OS of the doublet plus EGFRi cohort were 71.3% (95% CI, 65.2-78.2), 12.3 months (95% CI, 11.3-13.2), and 32.3 months (95% CI, 28.6-35.9), respectively.

After the random case-control matching, 32 patients from the doublet plus EGFRi cohort and 32 from the triplet plus bevacizumab cohort were paired according to all the selected variables.

Median PFS of the doublet plus EGFRi cohort was 13.6 months (95% CI, 8.9-31.7; 26 events), while median PFS of the triplet plus bevacizumab cohort was 16.1 months (95% CI, 12.1-36.8; 28 events), without statistically significant difference ($P = 0.621$).

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Table 1 Patients' Characteristics

	Overall (n = 718) N (%)	Doublet Plus EGFRi (n = 686) N (%)	Triplet Plus Bevacizumab (n = 32) N (%)	$\chi 2$ Test
Age, (y)				
Median	63	64	54	$P < .0001$
Range	28 – 84	28-84	31-72	
Non-elderly (<63 yo)	337 (46.9)	309 (45.0)	28 (87.5)	
Elderly (≥63 yo)	381 (53.1)	377 (55.0)	4 (12.5)	
Gender				
Male	445 (62.0)	426 (62.1)	19 (59.4)	$P = .7565$
Female	273 (38.0)	260 (37.9)	13 (40.6)	
ECOG PS				
0	441 (61.4)	412 (60.1)	29 (90.6)	$P = .0023$
1	257 (35.8)	254 (37.0)	3 (9.4)	
≥2	20 (2.8)	20 (2.9)	-	
Primary tumor location				
Left colon	433 (60.3)	411 (59.9)	22 (68.8)	$P = .318$
Rectum	285 (39.7)	275 (40.1)	10 (31.3)	
Previous adjuvant chemotherapy				
No	536 (75.8)	514 (75.5)	22 (84.6)	$P = .565$
Fluoropyrimidine only	85 (12.0)	83 (12.2)	2 (7.7)	
Fluoropyrimidine + oxaliplatin	86 (12.2)	84 (12.3)	2 (7.7)	
Primary tumor resection				
No	181 (25.2)	176 (25.7)	5 (15.6)	$P = .197$[a]
Yes	534 (74.4)	507 (73.9)	27 (84.4)	
NA	3 (0.4)	3 (0.4)	-	
Oligometastatic disease according to ESMO definition				
No	465 (64.8)	444 (64.7)	21 (65.6)	$P = 1.000$
Yes	253 (35.2)	242 (35.3)	11 (34.4)	
Metastatic sites (primary tumor excluded)				
1	371 (51.7)	351 (51.2)	20 (62.5)	$P = .210$
> 1	347 (48.3)	335 (48.8)	11 (37.5)	
Liver-limited disease (no lymph node metastases)				
No	476 (66.3)	463 (67.5)	13 (40.6)	$P = .002$
Yes	242 (33.7)	223 (32.5)	19 (59.4)	

[a] Computed among evaluable patients only.

Median OS of the doublet plus EGFRi cohort was 30.2 months (95% CI, 14.4-69.5; 18 events) while median OS of the triplet plus bevacizumab cohort was 38.1 months (95% CI, 33.1-101.1; 15 events), with a statistically significant difference ($P = 0.028$; Table 2, Figure 1).

The ORR was 65.6% (95% CI, 46.8-81.4) and 90.6% (95% CI, 74.9-98.0) in the doublet plus EGFRi and the triplet plus bevacizumab cohort, respectively, with a statistically significant difference ($P = .016$). Secondary resection rate differed significantly between the doublet plus EGFRi and the triplet plus bevacizumab cohorts (18.8% and 46.9%, respectively, $P = 0.016$; Table 2)

Among patients who underwent surgery with curative intent, median postresection PFS was 14.1 months (95%CI, 0.36-20.3; 9 events) and 11.3 months (95% CI, 0.34-26.6; 4 events) for the doublet plus EGFRi and the triplet plus bevacizumab cohort, respectively ($P = .439$), while median postresection OS was 47.7 months (95% CI, 25.2-47.7; 4 events) for the doublet plus EGFRi cohort and not reached (0 events) for the triplet plus bevacizumab cohort ($P = .394$; Table 2).

Safety Analysis

The safety profile in the overall population according to each cohort is summarized in Table 3. Triplet plus bevacizumab cohort was associated with a higher incidence of G3-4 neutropenia (25.0% vs 12.5%, $P = .041$). Two (6.3%) febrile neutropenia cases, fatal in 1 patient, occurred in the triplet plus bevacizumab cohort, and 2 (0.3%) treatment-related death occurred in the doublet plus EGFRi cohort.

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Figure 1 PFS (A) and OS (B) Kaplan–Meir estimate curves in the case-control matching population.

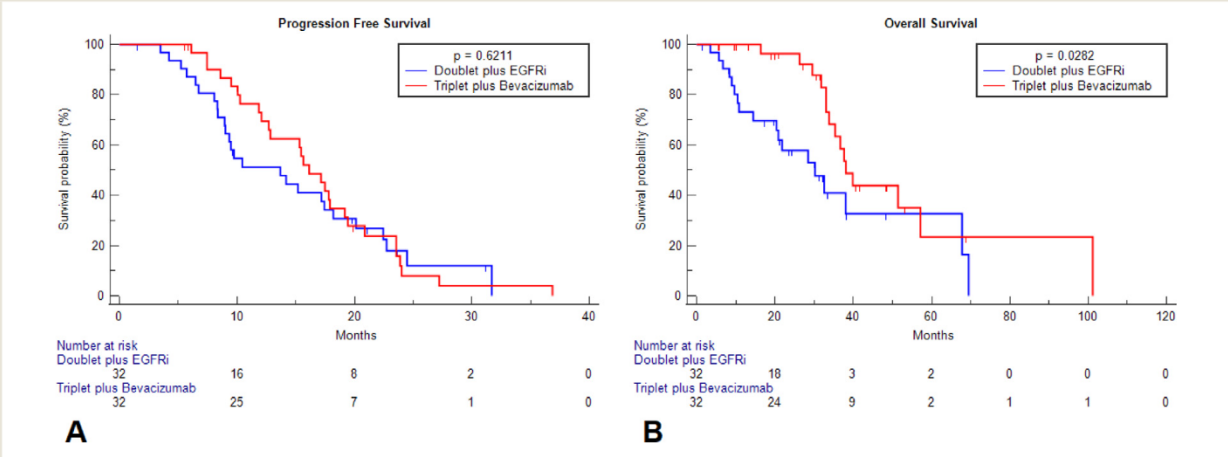

Table 2 Case-Control Matching for PFS, OS, Postresection PFS, Postresection OS, ORR, and Secondary Resection Rate

Doublet Plus EGFRi (n = 32)	Triplet Plus Bevacizumab (n = 32)	Log Rank
mPFS (95% CI) [events]		
13.6 mo (8.9-31.7)[26]	16.1 mo (12.1-36.8)[28]	*P* = .621
mOS (95%CI) [events]		
30.2 mo (14.4 -69.5)[18]	38.1 mo (33.1-101.1)[15]	*P* = .028
Median postresection PFS (95% CI) [events]		
14.1 mo (0.36-20.3)[9]	11.3 mo (0.34-26.6)[4]	*P* = .440
Median postresection OS (95% CI) [events]		
47.7 mo (25.2-47.1)[4]	Not reached [0]	*P* = .395
ORR [response ratio] (95% CI)		
65.6% [21/32] (46.8-81.4)[a]	90.6% [29/32] (74.9-98.0)*	*P* = .016
Secondary resection rate [response ratio]		
18.8% [6/32]	46.9% [15/32]	*P* = .016

Abbreviations: ORR = objective response rate; OS = overall survival; PFS = progression-free survival.
[a] Binomial confidence interval.

Table 3 Chemotherapy-Related Adverse Events (AEs) in the Overall Population

AEs, n (%)	Doublet Plus EGFRi (n = 686) N (%)		Triplet Plus Bevacizumab (n = 32) N (%)		$\chi 2$ Test	
	Any Grade	G3-G4	Any Grade	G3-G4	Any Grade *P*Value	G3-G4 *P*Value
Non-hematological[a]	356 (51.9)	34 (5)	21 (65.6)	1 (3.1)	.128	.638
Diarrhea	323 (47.1)	35 (5.1)	19 (59.4)	3 (9.4)	.174	.291
Peripheral neuropathy[b]	212 (60.4)	19 (5.4)	20 (62.5)	2 (6.3)	.816	.842
Hematological[c]	308 (44.9)	24 (3.5)	16 (50.0)	0 (0)	.571	.282
Neutropenia	322 (46.9)	86 (12.5)	20 (62.5)	8 (25.0)	.085	.041

[a] Diarrhea and peripheral neuropathy excluded.
[b] Among patients treated with oxaliplatin.
[c] Neutropenia excluded.

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Table 4 Postprogression Treatments in the Overall Population

	Overall (n = 718) N (%)	Doublet Plus EGFRi (n = 686) N (%)	Triplet Plus Bevacizumab (n = 32) N (%)	$\chi 2$ Test
Progression events to first line	560 (78.0)	532 (77.6)	28 (87.5)	$P = .184$
Second line treatment				
No	103 (18.5)	103 (19.5)	0 (0.0)	P = 0.010
Yes	453 (81.5)	425 (80.5)	28 (100)	
Second line treatment - type				
Triplet plus bevacizumab	3 (0.7)	0 (0.0)	3 (10.7)	$P < .001$
Monotherapy or doublet + bevacizumab	244 (53.4)	238 (55.5)	6 (21.4)	
FOLFIRI-aflibercept	68 (14.9)	66 (15.4)	2 (7.1)	
Monotherapy or doublet + anti-EGFR	76 (16.6)	61 (14.2)	15 (53.6)	
Regorafenib	11 (2.4)	19 (2.3)	1 (3.6)	
Other	55 (12.9)	54 (12.6)	1 (3.6)	
Progression events to second line	368 (82.3)	346 (82.2)	22 (84.6)	$P = .753$
Third line systemic therapy	278 (75.5)	258 (74.6)	20 (90.9)	$P = .084$
Fourth line systemic therapy	125 (51.4)	115 (50.4)	10 (66.7)	$P = .223$

Abbreviation: mAb = monoclonal antibody.

Postprogression Treatments

Overall, 425 of 532 (80.5%) and 28 of 28 (100%) of patients that progressed to doublet plus EGFRi and triplet plus bevacizumab treatment, respectively, underwent to a second-line systemic therapy ($P = .010$). Table 4 summarized maintenance and further-line treatments characteristics.

Discussion

This observational retrospective study intends to provide further data outside the clinical trial framework. To the best of our knowledge this is the first study aimed at evaluating the clinicians' attitude to and comparing the effectiveness of a doublet plus EGFRi and a triplet plus bevacizumab regimen as first line regimen in *RAS* and *BRAF* wild-type mCRC patients treated outside of a clinical trial.

A recent propensity score-based analysis of 317 left-sided *RAS* and *BRAF* wild-type mCRC patients treated with either FOLFOX plus panitumumab (185 patients) or FOLFOXIRI (or variants) plus bevacizumab (132 patients) within 5 randomized phase 2/3 clinical trials (Valentino, TRIBE, TRIBE2, STEAM, and CHARTA) found no statistically significant differences in terms of activity and efficacy, even if FOLFOXIRI plus bevacizumab was associated with numerically higher PFS (mPFS, 13.3 vs. 11.4 months, $P = .11$), OS (mOS, 33.1 vs. 30.3 months, $P = .14$), secondary resection rate (22% vs. 18%, $P = .51$), as well as postresection PFS (mPFS, 12.5 vs. 9.6 months, $P = .15$) and postresection OS (3-year OS rate 88.7% vs. 66.4%, $P = .06$) compared to FOLFOX-panitumumab. As expected, this trending benefit was accompained by a higher incidence of G3-4 chemotherapy-related AEs, especially neutropenia.[18]

The first result of the study to be discussed is the preponderance of the use of the doublet plus EGFRi over the triplet plus bevacizumab regimen. It reflects both the actual guidelines recommendations and the clinicians attitude, in clinical practice, in handling an intensive regimen, usually reserved to fit patients affected by aggressive disease with poor prognostic features (ie, *RAS* or *BRAF* mutations, right sidedness, high disease burden).[1, 8, 11] Concordantly, patients in the triplet plus bevacizumab cohort were younger and with slightly better ECOG-PS compared to patients from the doublet plus EGFRi cohort. Intriguingly, patients within the triplet plus bevacizumab cohort were more likely to be affected by liver-limited disease, with no differences according to tumor burden. The better clinical condition, the higher rate of liver-limited disease, together with a higher ORR, might have led to higher secondary resection rate in favor of the triplet plus bevacizumab. The retrospective nature of the analysis and the absence of a centralized radiological revision might have led to an underestimation of the baseline condition of resectability and to an overestimation of the response rate, at least in part explaining the discrepancies with data from clinical trials. However, most patients were evaluated within a multidisciplinary team for baseline metastases resectability, according to international guidelines recommendations and clinical evidence.[1, 19] In this respect, including R1 resection may have contributed to the higher radical resection rate in our study population compared to data from clinical trials.[18]

The higher rates of surgery with radical intent and of post-induction maintenance treatment, might have resulted in a trend toward better PFS, postresection RFS and postresection OS, enabling more patients to undergo second and further lines of treatment at disease relapsing, therefore, contributing to improved OS in the triplet plus bevacizumab respect to the doublet plus EGFRi cohort. On the other hand, patients within the doublet plus EGFRi population were older, with worst ECOG-PS and a lower rate of liver-limited disease and this might have affected activity as well as effectiveness clinical outcomes in this cohort.

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In this respect, preclinical and clinical evidence show a higher prevalence of uncommon genomic alterations (i.e. *HER2* amplification/activating mutations; *MET* amplification, *PIK3CA* exon 20, *PTEN*, and *AKT1* mutations; *ROS1/NTRKs/ALK/RET* rearrangements) related to EGFRi primary resistance in left-sided *RAS/BRAF* wild-type mCRC.[6, 20-22] It is likely that a molecular hyperselection of this population, which to date is not recommended in clinical practice, might have resulted in different activity and effectiveness outcomes in the doublet plus EGFRi cohort. Moreover, preclinical studies showed that acquired resistance to EGFRi derives from the emergence of novel mutations in the *RAS* gene family and that *KRAS* mutant isoforms could be a VEGF expression inducer,[23, 24] effectively targetable by antiangiogenic-based therapies as second line treatment in left-sided *RAS/BRAF* wild-type mCRC patients progressed to an EGFRi-based first line regimen.[25] On the other hand, the antiangiogenic bevacizumab in combination with a triplet regimen showed improved activity and efficacy over a doublet regardless of baseline clinical characteristics and *RAS* or *BRAF* mutational status,[8] providing consistent and even higher benefit in that subgroup of mCRC patients with better prognosis (i.e. *RAS/BRAF* wild-type, left sidedness, low number of metastatic sites or condition of oligometastatic disease), that to some extent our study population reflects.[4, 26]

Concerning safety data, results from this analysis are concordant with those reported in clinical trials and the expected higher incidence of chemotherapy-related AEs following the use of triplet plus bevacizumab, especially neutropenia, was confirmed. On the other hand, the deep differences between anti-angiogenics and EGFRi class-specific AEs in terms of potential impact on tolerance and quality of life of mCRC patients treated in clinical trials as well as in daily clinical practice are well known.[27, 28]

The small sample size of the triplet plus bevacizumab cohort and lack of pertaining data prevented an analysis of the potential predictive role of histology, as well as of microsatellite instability condition, which would have been of interest, since some evidence suggest EGFRi could be less effective with respect to bevacizumab-based regimens in mucinous and in microsatellite instability tumors.[29, 30] Because of the obvious limitations of this study, including its retrospective design and the related selection bias, the results must be taken with caution and no conclusive considerations are allowed.

Conclusion

Although a doublet plus EGFRi remains the recommended upfront regimen in left-sided *RAS* and *BRAF* wild-type mCRC patients, a triplet plus bevacizumab might be at least equally active and effective in properly selected cases, especially in younger patients, with good ECOG-PS and liver-limited disease to convert to radical surgery. Further analysis with a larger sample size and a prospective translational design are certainly needed to better define and personalize the first line strategy in left-sided *RAS* and *BRAF* wild-type mCRC patients. In this respect, results from the ongoing first-line, randomized phase 2/3 trials aimed at comparing doublets plus EGFRi and triplets plus EGFRi in unresectable mCRC (TRIPLETE, NCT03231722 and PANIRINOX, NCT02980510) are certainly awaited, as they will potentially represent additional milestones, useful for the decision-making in the first-line treatment of mCRC.

Clinical Practice Points

- Data comparing activity, efficacy and safety of a doublet plus EGFRi and a triplet plus bevacizumab regimen as first-line treatment in left-sided RAS/BRAF wild-type metastatic colorectal cancer patients are lacking
- In this retrospective multicentre "real-life" study of clinicians attitude, we found that the great majority of the left-sided *RAS/BRAF* wild-type mCRC patients have been treated with a doublet plus EGFRi, while a triplet plus bevacizumab regimen was reserved to selected cases, especially to younger patients, with good ECOG-PS and liver-limited disease to convert to radical surgery
- Although a doublet plus EGFRi remains the recommended upfront regimen in left-sided RAS and BRAF wild-type mCRC patients, a triplet plus bevacizumab seems to be at least equally active and effective in properly selected patients, with a manageable safety profile

Informed Consent

All patients alive at the time of data collection provided an informed consent to participate to this retrospective observational noninterventional study.

Ethical Statement

All patients alive at the time of data collection provided informed consent to participate to this retrospective observational non-interventional study. The procedures followed were in accordance with the precepts of Good Clinical Practice and the declaration of Helsinki. The study was approved by the respective local ethical committees on human experimentation of each institution, after previous approval by the coordinating center (Comitato Etico delle Province di L'Aquila e Teramo, protocol number 21, approved on July 16, 2020).

Authors' Contributions

All authors contributed to the publication according to the ICMJE guidelines for the authorship. All authors read and approved the manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Sharing

The datasets used during the present study are available from the corresponding author upon reasonable request.

Disclosure

Alessandro Parisi reported receiving advisory board fees from GSK. Alessio Cortellini reported receiving consulting/advisory board fees from Astrazeneca, MSD, Roche and BMS; speakers' fee from Novartis, Astellas, MSD, Astrazeneca. Angelica Petrillo reported receiving fees from Eli-Lilly, MSD and Servier. Riccardo Giampieri reported receiving fees from Amgen and Servier and advisory board fees from Amgen, Servier, Bayer and Merck-Serono. The other authors have declared no conflicts of interest

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Acknowledgments

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors; it is aimed at improving the clinical practice. The study meets all the Italian nonprofit requirements.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clcc.2021.07.003.

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